LD0268 NP

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Anastasia P. Winslow		May 25th, 2006
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
FRANCIS LEE, ET AL
APPLICATION NO: **10/091061**
FILED: **03/05/2002**
FOR: **COMBINATION OF EPOTHILONE ANALOGS AND CHEMOTHERAPEUTIC AGENTS FOR THE TREATMENT OF PROLFERATIVE DISORDERS.**

ART UNIT: **1617**
EXAMINER: **CHONG, YONG SOO**

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Sir:

Enclosed herewith is original and one copy of the Appeal Brief in the above-identified application.

☒ Please charge Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company in the amount of $500 for payment of the appeal fee. An additional copy of this paper is here enclosed. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

☐ Enclosed is a Petition for Extension of Time.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000

Anastasia P. Winslow
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Reg. No. 40,875
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Date: May 25, 2006

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Anastasia P. Winslow		May 25, 2006
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

LEE

APPLICATION NO: **10/091,061**

FILED: **MARCH 5, 2002**

Art Unit: **1617**

Examiner: JIANG, SHAOJIA A

FOR: **COMBINATION OF EPOTHILONE ANALOGS AND CHEMOTHERAPEUTIC AGENTS FOR THE TREATMENT OF PROLIFERATIVE DISEASES**

APPEAL BRIEF ON BEHALF OF APPELLANT-APPLICANT

ON APPEAL FROM FINAL REJECTION OF CLAIMS 117 TO 130 MAILED DECEMBER 27, 2005

05/31/2006 SDENBOB1 00000049 193880 10091061

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Submitted by:
Anastasia P. Winslow (Reg. 40,875)

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000

I. REAL PARTY IN INTEREST

The real party in interest is Bristol-Myers Squibb Company (BMS), a corporation organized and existing under the laws of Delaware and having an office and place of business at P.O. Box 4000, Princeton, NJ, 08543. The inventor, Francis Lee, assigned his entire right, title, and interest in this application to BMS by assignment recorded at Reel No. 012680, Frame 0464, on March 5, 2002. 37 C.F.R. § 41.37(c)(1)(i).

II. RELATED APPEALS AND INTERFERENCES

The appellant or his legal representatives are not aware of any related appeals and/or interferences at this time. 37 C.F.R. § 41.37(c)(1)(ii).

III. STATUS OF CLAIMS

Claims 101-111 and 113-130, set forth in the Claims Appendix, stand rejected in this application.

Claims 117-130 are on appeal.

Pending claims 101-111 and 113-116 are not being appealed.

Claims 1-100 and 112 were previously canceled.

The subject matter of the canceled claims (claims 1-100 and 112), is being pursued in divisional application Serial No. 10/850,072, filed on May 20, 2004; and in divisional application Serial No. 11/009,579, filed on December 10, 2004. 37 C.F.R. § 41.37(c)(1)(iii)

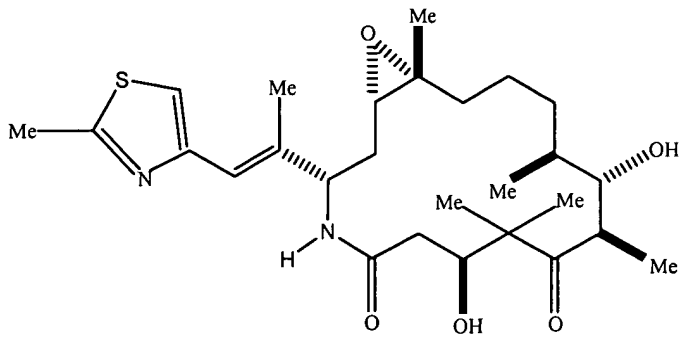
IV. STATUS OF AMENDMENTS

Claims 101-111 and 113-130 were finally rejected in the December 27, 2005 final Office Action. No amendments were filed since this final rejection. 37 C.F.R. § 41.37(c)(1)(iv). Only claims 117-130 are an appeal.

V. SUMMARY OF INVENTION

The claimed invention on appeal is directed to methods of treating cancer by administering a combination of agents having a synergistic or enhanced anti-cancer

effect, wherein the combination comprises the agent capecitabine (known as Xeloda™) and Compound (1). Compound (1) is [1S- [1R*,3R*(E),7R*,10S*,11R*,12R*, 16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione (known as "ixabepilone"), and has the following formula:



See, inter alia, page 2, line 32 to page 5, line 2; page 17, lines 15-29; page 20, lines 25-30; page 22, line 20; and page 25, lines 10-35.

Independent claim 117 is directed to a method of treating certain cancers, comprising administering a therapeutically-effective combination of a dosage unit of capecitabine and a dosage unit of Compound (1), wherein the administration will provide a greater anti-cancer effect than the effect obtainable with either the dosage unit of capecitabine or the dosage unit of Compound (1) alone. *See, inter alia,* page 9, lines 7-11; page 17, lines 15-29; page 20, lines 25-30; page 22, line 20; page 25, lines 10-35; and page 38, line 30 to page 41, line 12. The cancers recited in claim 117 are metastatic breast cancer, lung cancer, pancreatic cancer, ovarian cancer, prostate cancer, colon cancer, and small cell lung cancer.

Claims 118-125 depend upon claim 117, and thus, these claims incorporate the method comprising administering the combination of Compound (1) and capecitabine to achieve an enhanced anti-cancer effect. These claims are also further directed to particular metastatic breast cancers (claims 118-120), the timing of administration (claims 121-123), and the form of administration (*e.g.,* via oral or parenteral administration). *See, inter alia,* page 26, lines 1-4; and page 21, lines 1-18.

Independent claim 126 is directed to methods of treating certain cancers, comprising administering a synergistically-effective combination of capecitabine and Compound (1). *See, inter alia,* page 9, lines 7-11; page 17, lines 15-29; page 20, lines 25-30; page 22, line 20; and page 25, lines 10-35. The cancers recited in claim 117 are metastatic breast cancer, lung cancer, pancreatic cancer, ovarian cancer, prostate cancer, colon cancer, and small cell lung cancer.

Claims 127-130 depend upon claim 126 and thus, these claims incorporate the method comprising administering the combination of Compound (1) and capecitabine to achieve a synergistic, anti-cancer effect. These claims are also further directed to use of the combination to treat metastatic breast cancer (claim 127), and cancers refractory (128), resistant (129), or sensitive (130) to taxane treatment. *See, inter alia,* page 26, lines 1-4; and page 21, lines 1-18.

VI. GROUNDS OF REJCTION TO BE REVIEWED ON APPEAL

The following grounds of rejection are to be reviewed on this appeal:

1. Whether claims 117-125 are nonobvious under 35 U.S.C. 103(a) as being patentable over Danishefsky (US 6,867,305) in view of Miwa *et al.* (*European Journal of Cancer*, Vol. 34, No. 8, pp 1274-1281, 1998).

2. Whether claims 117-130 are nonobvious under 35 U.S.C. 103(a) as being patentable over Vite (WO 99/02514) in view of The Merck Index, (12th Edition, pp MISC-10, 1996) and Miwa *et al.* (*European Journal of Cancer*, Vol. 34, No. 8, pp 1274-1281, 1998).

VII. ARGUMENT

POINT ONE

CLAIMS 117-125 WERE IMPROPERLY REJECTED UNDER 35 U.S.C. § 103(a) AS BEING UNPATENTABLE OVER DANISHEFSKY (US PAT. 6,867,305) IN VIEW OF MIWA *ET AL.* (*EUROPEAN JOURNAL OF CANCER*, VOL. 34, NO. 8, PP 1274-1281, 1998).

The Examiner's first ground of rejection was applied to Claims 117 to 125 (collectively), and is based upon Section 103(a), 35 U.S.C. § 103(a), in view of US Pat. 6,867,305 to Danishefsky *et al.* (hereinafter "Danishefsky"), as combined with Miwa *et al.* (*European Journal of Cancer*, Vol. 34, No. 8, pp 1274-1281, 1998) (hereinafter "Miwa"). The Examiner has not applied this rejection to claims 126 to 130. This rejection must be reversed as the examiner has not established a *prima facie* case of obviousness.[1]

The obviousness inquiry under *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S. Ct. 684, 693 (1966), requires that the decision-maker consider: (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, (3) the level of ordinary skill in the field at the time the invention was made, and (4) objective evidence of secondary considerations. *Id.; see also Para-Ordnance Mfg. v. SGS Importers Intern.*, 73 F.3d 1085, 1088, 37 USPQ2d 1237 (Fed. Cir. 1995). In considering the scope and content of the prior art, the *full* disclosures must be considered including sections that teach away from the claimed invention. *See W.L. Gore & Associates, Inc. v, Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. The examiner must meet three basic requirements to establish a *prima facie* case:

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[1] Moreover, for the reasons set forth in Point Three, *infra*, applicant has rebutted any alleged obviousness claim.

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one or ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP 2143

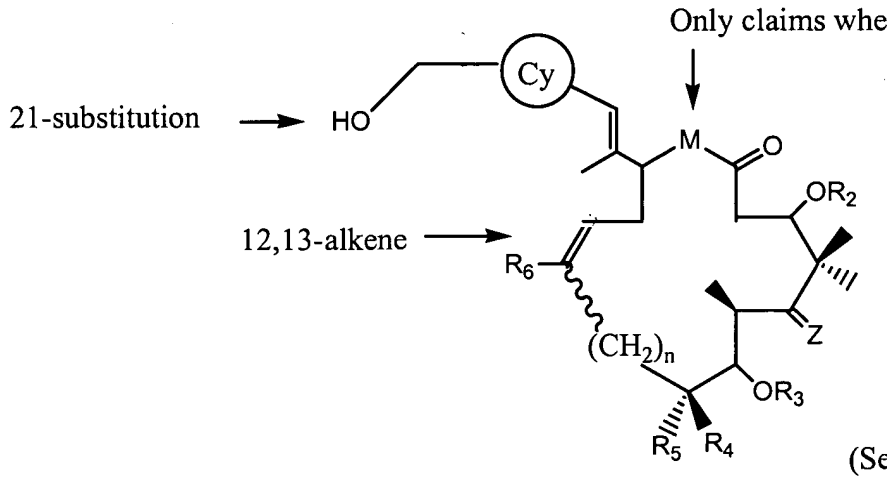
See also In re Chu, 66 F.3d 292, 36 USPQ2d 1089, 1094 (Fed. Cir. 1995); *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443, 1444-46 (Fed. Cir. 1992); and MPEP § 2143. The burden of satisfying these requirements rests squarely with the PTO. *See Ex Parte Skinner*, 2 USPQ2d 1788, 1789 (Bd. Pat. App. & Inter. 1986); MPEP § 2142.

Here, these requirements are not met. There is no motivation to combine Danishefsky and Miwa, but rather, the examiner has improperly employed hindsight to selectively combine parts of these references, using appellant's disclosure. Additionally, there is no reasonable expectation of success in the prior art. Specifically, there is no reasonable expectation of success in the art for an enhanced beneficial effect upon administration of Compound (1) in combination with capecitabine. Below, the scope and content of the prior art first will be discussed, followed by the reasons why a *prima facie* case is not established.

A. SCOPE AND CONTENT OF PRIOR ART

(1) Danishefsky

Danishefsky is directed to a genus of alleged novel epothilone analogs having the following formula:



(See, cols. 3-4, col 124)

The invention of Danishefsky is thus directed towards certain epothilone analogs wherein the epoxide is replaced with a 12,13-alkene group (referred to by Danishefsky as 12,13-desoxyepothilone analogs), as disclosed in column 3, line 26 to column 4, line 38. For example, in Danishefsky, the background section describes the prior art as including compounds having structure 1 (col. 2, lines 1-19), with an epoxide at the 12,13-position. Additionally, the prior art is described as including compounds having structure 2 (col. 2, lines 20-35), with a 12,13-alkene group, which are also referred to by Danishefsky as "12,13-desoxyepothilones". The disclosure of Danishefsky is directed to compounds lacking the epoxide as in structure 2 (cols. 3-4), and claims only such compounds wherein M is O (col. 124).

Danishefsky discloses, but *teaches against*, the use of epothilone analogs having an epoxide group at the 12,13-position as in the prior art,[2] *further teaches against* use of an unsubstituted C21 methyl group,[3] and *further teaches against* use of an aza-

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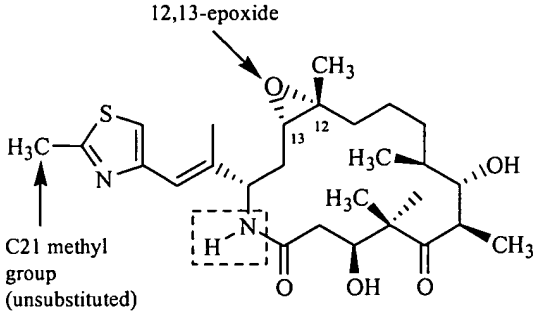
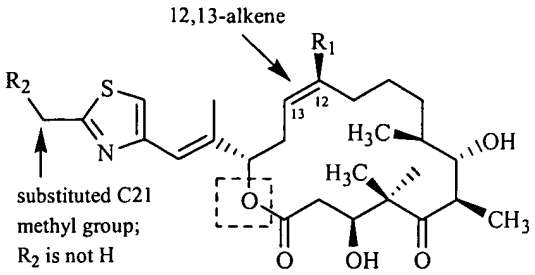
[2] *E.g.*, at col. 2, lines 38-59, Danishefsky states: "It has recently been demonstrated during the course of these and other studies that 12,13-desoxyepothilone B (2b, dEpoB), manifests a more promising therapeutic profile than does epothilone B (1b, EpoB). Specifically, it has been found that dEpoB exhibits an enhanced therapeutic range relative to epothilone B due to reduction in toxic dose levels ..." (col. 2, lines 38-59).

[3] E.g., at col. 3, lines 12-23), Danishefsky states: "in view of the potential benefits of having a functional handle at C21, and based upon the recognition by the present

modification (*see*, col. 98, line 62 to col. 100, discussed further, *infra*). Compound (1) of the present invention has all these features, as illustrated below:



Compound (1)



12,13-desoxyepothilone analogs of Danishefsky

Danishefsky specifically teaches against the use of Compound (1). (Col. 100, lines 43-45).

Danishefsky discloses Compound (1) (referred to in Danishefsky as aza-epoB), not as a novel compound of its invention, but as a known compound that is used in comparative examples to allegedly show benefits of Danishefsky's compounds (*e.g.*, col. 98, line 76 to col. 99, line 7). In addition, Danishefsky discloses methods of synthesizing epothilone analogs via total synthesis (the epothilones being naturally-occurring compounds that are obtained via natural strain fermentation), and illustrates a total synthesis method allegedly useful for making Compound (1). (Cols. 107-08).

More particularly, Danishefsky comments on Compound (1) (referred to therein as aza-epoB), as compared with a 12,13-alkene compound (epothilone D), as follows:

> aza-EpoB had markedly reduced activity in our multi-drug resistant cell lines (CCRF-CEM/$_{VBL100}$, CCRM-CEM/$_{VM1}$, and CCRF-CEM/$_{Taxol}$ as compared with dEpoB. (col. 98, line 67 to col. 99, line 7).

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inventors of the superior therapeutic profile of 12,13-desoxyepothilones, it would be desirable to develop novel synthetic methods to enable facile access to 12,13-deoxy, 21-hydroxy analogues of epothilone."

Regarding Compound (1), as compared with 12,13-alkene compounds, Danishefsky further states:

> As depicted in FIG. 34 treatment of the mice with aza-EpoB (6 mg/kg) inhibited tumor growth but did not lead to a reduction in the size of the tumor. In contrast, further treatment of the same mice with dEpoF (30 mg/kg) readily induced reduction in the size of the tumor to the point of remission. (col. 99, lines 54-59).

Danishefsky concludes this section with an explicit teaching against the use of Compound (1):

> Whereas, aza-EpoB was more active than dEpoB in nonresistant cell lines, *it proved ineffective when extended to in vivo models.* (col. 100, line 43-45) (emphasis supplied).

Also disclosed in Danishefsky are methods of treating cancer using the alleged, novel epothilone analogs in combination with other therapies. Danishefsky highlights a number of combinations as potentially useful. In particular, at column 10, line 20, Danishefsky states the *inventive compounds, i.e.*, those bearing the 12,13-alkene group – not Compound (1) -- may be used in combination with *adriamycin, vinblastin, or paclitaxel, or combinations thereof* (col. 10, line 20). Danishefsky further highlights that the inventive compounds may be used with *Taxol®, vinblastin, adriamycin, and camptothetcin* (col. 30, l. 32). After highlighting those specific combinations, Danishefsky provides a generalized disclosure of combinations for its inventive compounds -- which bear the 12,13 alkene, not Compound (1)) -- as follows:

> It will also be appreciated that the compounds and pharmaceutical compositions *of the present invention* can be employed in combination therapies, that is, the compounds and pharmaceutical compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another anticancer agent), or they may achieve different effects (e.g., control of any adverse effects).

> For example, other therapies or anticancer agents *that may be used in combination with the inventive anticancer agents of the present invention* include surgery, radiotherapy (in but a few examples, .gamma.-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes, to name a few), endocrine therapy, biologic response modifiers (interferons, interleukins, and tumor necrosis factor (TNF) to name a few), hyperthermia and cryotherapy, agents to attenuate any adverse effects (e.g., antiemetics), and other approved chemotherapeutic drugs, including, but not limited to, alkylating drugs (mechlorethamine, chlorambucil, Cyclophosphamide, Melphalan, Ifosfamide), antimetabolites (Methotrexate), purine antagonists and pyrimidine antagonists (6-Mercaptopurine, 5-Fluorouracil, Cytarabile, Gemcitabine), spindle poisons (Vinblastine, Vincristine, Vinorelbine, Paclitaxel), podophyllotoxins (Etoposide, Irinotecan, Topotecan), antibiotics (Doxorubicin, Bleomycin, Mitomycin), nitrosoureas (Carmustine, Lomustine), inorganic ions (Cisplatin, Carboplatin), enzymes (Asparaginase), and hormones (Tamoxifen, Leuprolide, Flutamide, and Megestrol), to name a few. For a more comprehensive discussion of updated cancer therapies see, http://www.nci.nih.gov/, a list of the FDA approved oncology drugs at http://www.fda.gov/cder/cancer/druglistframe.htm, and The Merck Manual, Seventeenth Ed. 1999, the entire contents of which are hereby incorporated by reference. (Emphasis supplied)

Notably, included within this list is the entire Merck Manual, incorporated by reference, and 5-fluorouracil (hereinafter "5-FU") (at col. 60, line 7).

(2) Miwa

Miwa discloses the metabolic pathway that converts the prodrug capecitabine to the anticancer agent 5-FU. The metabolic pathway, illustrated in Figure 4, at page 1278 of Miwa, involves a cascade of three essential enzymes, *i.e.*, carobyxlesterase, cyd deaminase, and dThdPase (*i.e.*, thymidine phosphorylase). Miwa discloses that capecitabine was designed by investigating the localization of these enzymes in tumor tissues. Miwa further states that capecitabine is finally converted in the last step to 5-FU by dThdPase in tumors and should be safer and more effective than 5-FU (pp. 1274, 1280).

B. THERE IS NO MOTIVATION TO MODIFY AND COMBINE THE CITED REFERENCES AS THE CONTENT OF THE PRIOR ART, WHEN CONSIDERED IN ITS ENTIRETY, TEACHES AWAY FROM THE CLAIMED INVENTION

The Examiner's obviousness rejection as applied to claims 117-125 involves a selection of Compound (1) from Danishefsky, then a selection of 5-FU from the laundry list of anti-cancer agents (including the Merck Manual) at col. 60 of Danishefsky, then a modification of 5-FU to capecitabine based upon Miwa's comment that capecitabine should be safer than 5-FU.

When applying 35 U.S.C. §103, one basic tenet of patent law that must be honored is that references must be considered as a whole and must suggest the *desirability* of making the proposed combination. *See* MPEP 2141. In this vein, it is inappropriate to "pick and choose among the individual elements of assorted prior art references to recreate the claimed invention." *Smithkline Diagnostic Inc. v. Helena Labs Corp.,* 859 F.2d 878, 887, 8 USPQ2d 1468, 1475 (Fed. Cir. 1988).

Here, the examiner has not provided any motivation or suggestion why one skilled in the art would select Compound (1) from the various epothilones and analogs disclosed in Danishefsky. Numerous epothilone analogs are encompassed within the various genuses of compounds represented by the structures at cols. 3-4 and cols. 31-37 of Danishefsky. Notably, Compound (1) which bears the 12,13-epoxide, does not fall within any one of Danishefsky's general formulae, nor does it fall within any one of Danishefsky's more narrow preferred subgenuses. With regard to Compound (1), Danishefsky teaches against selecting this compound – in principle based on structure-activity-relationships (SAR) and directly based upon comparative data. Specifically, Danishefsky states, among other things, that Compound (1) *"proved ineffective when extended to in vivo models"* (col. 100, line 43-45) (emphasis supplied). Where, as here, the prior art teaches away from the claimed invention, this is "strong evidence of non-obviousness." *In re Hedges*, 783 F.2d 1038, 1041, 228 USPQ 685, 687 (Fed. Cir. 1986).

With regard to the combination of agents, the examiner has not established any motivation or suggestion for picking 5-FU to be used in combination with Compound (1). Rather, Danishefsky highlights that its *inventive* compounds, not Compound (1), may be used in combination with Taxol® (paclitaxel), vinblastin, adriamycin, and/or camptothetcin. In contrast, there is no motivation or suggestion why one skilled in the art would select 5-FU from the large list of therapies or other anticancer agents disclosed in Danishefsky, as well as those disclosed in The Merck Manual, Seventeenth Ed. 1999, whose entire contents were incorporated by reference into Danishefsky (col. 59, line 60 to col. 60 line 20). There further is no motivation in Danishefsky to then combine 5-FU with Compound (1), given Danishefsky's combinations are directed toward use with its inventive compounds, *i.e,* those bearing the 12,13-alkene group, not Compound (1).

The examiner has engaged in hindsight reconstruction by picking and choosing from Danishefsky a specific compound (Compound (1)), against Danishefsky's teachings, and then a specific anticancer agent (5-FU), disclosed for use with Danishefsky's inventive compounds (not Compound (1)), and then, armed with this selection of agents, the examiner has selectively identified Miwa to allege a basis to modify the disclosure of 5-FU in Danishefsky to capecitabine. A *prima facie* case of obviousness has not been established as the examiner is simply picking and choosing from the references using hindsight gained from applicant's disclosure.

Although the examiner asserts that capecitabine (which is enzymatically converted to 5-FU *in vivo*) is taught as being safer and more effective than 5-FU, this assertion does not address the issue of motivation or suggestion to select Compound (1), or to select 5-FU from the other disclosed therapies and anticancer agents to be used with Compound (1), nor does it provide a basis to believe capecitabine would have advantageous, enhanced beneficial effects in combination with Compound (1).

D. NO REASONABLE EXPECTATION OF SUCCESS IN THE PRIOR ART

Claims 117 to 125 recite an enhanced anti-cancer effect obtainable when Compound (1) is administered in combination with capecitabine, *e.g.*, as compared with when either compound is administered as a single agent. For a *prima facie* obviousness

conclusion, the reasonable expectation of success for this invention, as recited in the claims, must be found in the prior art, not in applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Here, there is no reasonable expectation of success for at least two independent reasons. First, Danishefsky teaches that Compound (1) *"proved ineffective when extended to in vivo models"* (col. 100, line 43-45) (emphasis supplied). Thus, there is no reasonable expectation of success in the cited prior art with use of Compound (1) in anti-cancer therapies.

Second, there is no suggestion that Compound (1) in combination with capecitabine, in particular, would achieve enhanced effects. Miwa discloses that three enzymes are needed to convert 5-FU to capecitabine. The prior art does not provide any indication or suggestion as to how Compound (1) may impact upon the presence or operation of these enzymes. While Miwa states capecitabine may be safer than 5-FU, it does not state that capecitabine and 5-FU are interchangeable, nor does it go the next step – the step taken by the examiner – to conclude that 5-FU and capecitabine are interchangeable and have the same effectiveness in any combinations with any additional anti-cancer agents even in view of potential drug-drug interactions or side-effect profiles. The examiner has lost sight of the fact that three enzymes are involved in the conversion of capecitabine to 5-FU, and an additional agent administered in combination could impact upon the levels, operation or effect of these enzymes. For the foregoing reasons, the examiner's rejection of claims 117 to 126 based upon Danishefsky in view of Miwa must be reversed.

POINT TWO

CLAIMS 117-130 WERE IMPROPERLY REJECTED UNDER 35 U.S.C. 103(a) AS BEING UNPATENTABLE OVER VITE (WO 99/02514) IN VIEW OF THE MERCK INDEX, (12TH EDITION, PP MISC-10, 1996) AND MIWA *(SUPRA)*.

The Examiner's second ground of rejection was applied to Claims 117 to 130 (collectively), and is based upon Section 103(a), 35 U.S.C. § 103(a), in view of WO 99/02514 to Vite *et al.* (hereinafter "Vite"), as combined with The Merck Index, 12th Edition, pp MISC-10, 1996, and Miwa (as above, Point I). This rejection must be reversed as the examiner has not established a *prima facie* case of obviousness in that (1) there is no suggestion or motivation to combine these reference teachings, (2) there is no reasonable expectation of success, and (3) the prior art reference (or references when combined) do not teach or suggest all the claim limitations. MPEP 2142-43; *In re Vaeck*, 947 F.2d at 488; *In re Chu*, 66 F.3d at 292; *In re Oetiker*, 977 F.2d 1at 443, 24 USPQ2d at 1444-46 (Fed. Cir. 1992).[4]

A. SCOPE AND CONTENT OF THE PRIOR ART

The examiner has admitted in the Office Action dated December 27, 2005 that "The prior art does not expressly disclose the employment of the instant particular compound in combination with the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine in a pharmaceutical composition and a method of treating cancer." (page 7, lines 2-5). Compound (1) is the "instant particular compound" in this statement. The examiner's second ground of rejection, like the first (discussed in Point I, above), is based upon "cherry-picking" selections from generalized references, and then a piecing of these selections together to arrive at applicant's invention.

(1) Vite

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[4] Moreover, for the reasons set forth in Points Three and Four, *infra*, applicant has rebutted any alleged obviousness claim.

WO 99/02514 to Vite *et al.* (hereinafter "Vite") discloses a genus of epothilone analogs (Structure V), which includes Compound (1) of the present invention. Vite also discloses Compound (1) as an Example.

Vite does not discuss combinations of Compound (1) with other specifically-named chemotherapeutic agents. Vite does not discuss 5-FU or capecitabine. Rather, Vite refers to combinations as follows:

> The compounds of this invention are also useful in combination with known anti-cancer and cytotoxic agents and treatments, including radiation. If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent within its approved dosage range. Compounds of formula V can be used sequentially with known anticancer or cytotoxic agents and treatment, including radiation when a combination formulation is inappropriate. Especially useful are cytotoxic drug combinations wherein the second drug chosen acts in a different phase of the cell cycle, e.g., S phase, than the present compounds of formula V, which exert their effects at the G_2-M phase. (*See* column 6, lines 18-31).
>
> e.g. Thymidilate Synthase Inhibitors
> DNA Cross Linking Agents
> Topoisomerase I and II Inhibitors
> DNA Alkylating Agents
> Ribonucleoside Reductase Inhibitors
> Cytotoxic Factors e.g. TNF-alpha or
> Growth factor inhibitors e.g. HER 2 receptor MAB's

(2) The Merck Index

The examiner has combined Vite with The Merck Index, 12th Edition, pp MISC-10, 1996. The examiner has cited only page MISC-10. However, the list of chemotherapy combinations in this reference continues to page MISC-11. This reference, which includes both pages MISC-10 and MISC-11, must be considered in its entirety. The reference, which is an appendix in The Merck Index, is titled "Cancer Chemotherapy Drug Regimens", and discloses "selected acronyms for combination cancer chemotherapy regimens comprising substances in *The Merck Index*". The list discloses 100 different combinations, including 9 combinations of two anticancer agents and 91 combinations of three to ten anticancer agents. Only 24 of these 100 combinations contain 5-FU. Neither Compound (1) nor capecitabine is identified.

(3) Miwa

This is the same Miwa reference discussed above with regard to the first ground of rejection. It discloses the metabolic pathway that converts the prodrug capecitabine to the anticancer agent 5-FU via three essential enzymes. Miwa does not disclose or suggest any combinations of agents.

B. THERE IS NO MOTIVATION TO COMBINE THE REFERENCES BUT INSTEAD THE EXAMINER HAS AGAIN ENGAGED IN A HINDSIGHT RECONSTRUCTION OF THE INVENTION WITH THE BENEFIT OF APPELLANT'S DISCLOSURE

Here, it is quite telling that the examiner is relying on a disclosure from The Merck Index, which lists 100 different combination therapies. The majority of these combinations (76 combinations) do not contain 5-FU, and none involve Compound (1). Among the 24 combinations containing 5-FU, the 5-FU is present in combinations with in some cases two, three, four and even five other anticancer agents. Clearly, this reference is no more than a laundry list of certain anticancer drug combinations and their components. The reference is silent regarding the choice of any particular combination, and especially silent regarding the choice of any individual anticancer agent from the multiple substances contained in the list. The reliance now placed upon The Merck Index reference, considering the many combinations listed on pages MISC-10 and MISC-11, to select a single anticancer agent from that reference, underscores that the examiner is engaging in hindsight reconstruction.

The Federal Circuit has emphasized that it will demand a "rigorous application of the requirement for a showing of the teaching or motivation to combine prior art cases." *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). This vigorous showing is necessary to guard against hindsight-based obviousness analyses. *Id.* To guard against use of hindsight, the examiner must make particular findings based on actual evidence that the prior art teaches the combination, and the "showing must be clear and particular." *Id.* at 1617. Here, no particular findings based on actual evidence have been made.

Instead, the Office Action argues that because 5-FU is known in combination cancer chemotherapy, it would have been obvious to combine it with Compound (1), since both are known for the same purpose. This is not evidence or particularized findings but a conclusory statement that is entirely inadequate to support a § 103 rejection. *See id.* (*citing In re Sichert*, 566 F.2d 1154, 1164, 196 USPQ 209, 217 (CCPA 1977)), and MPEP § 2143.01.

The examiner has further asserted that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose. However, this is an incorrect assertion of the law. As the Federal Circuit has long recognized, "[v]irtually all inventions are combinations and virtually all are combinations of old elements." *Environmental Designs, Ltd., v. Union Oil Co.*, 713 F.2d 693, 698, 218 USPQ 865, 870 (Fed. Cir. 1983). The notion, therefore, that combination claims can be declared invalid upon finding similar elements in separate prior art patents and piecing them together would destroy nearly all patents and is not the law. *See Smithkline, supra*, 8 USPQ2d at 1475 ("[a] holding that combination claims are invalid based merely upon finding similar elements in separate prior art patents would be 'contrary to statute and would defeat the congressional purpose in enacting Title 35'") (*quoting Panduit Corporation v. Dennison Manufacturing Co.*, 810 F.2d 1561, 1 USPQ2d 1593 (Fed. Cir.), *cert. denied*, 107 S. Ct. 2187 (1987)).

Contrary to the examiner's broad and inaccurate statement generally rejecting combination claims, a new combination of previously known elements is patentable where, as here, there is no teaching or suggestion in the art to support the particular claimed combination, or where the particular claimed combination proceeds contrary to teachings in the field. *See, e.g., Arkie Lures Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 43 USPQ2d 1294, (Fed. Cir. 1997) (reversing summary judgment conclusion of obviousness for a combination of a plastisol lure with salt, although both plastisol lures and salted bait were known); *see also Environmental Designs, supra*, 218 USPQ at 870 (rejecting obviouness argument even though "[a]ll the pieces of the present invention were known in the art"). Additionally, courts have held patentable combinations of

known elements where the particular combination has demonstrated unexpected properties. *See, e.g., Novo Industri A/S v. Travenol Labs.*, 677 F.2d 1202, 215 USPQ 412 (7th Cir. 1982) (upholding patentability of process involving combination of elements including a known species of fungus for producing cheese, as results with the particular combination of elements were unexpectedly good).

Here, the invention pertains to a combination of cytotoxic compounds useful for treating cancer, and thus, the invention implicates considerations for efficacy, accumulative side-effects, drug-drug interactions, possible contraindications, and other factors. The claims on appeal recite enhanced beneficial and synergistic anti-cancer effects upon administering a unique combination of two species of compounds – capecitabine and Compound (1). However, the examiner has merely consulted the Merck Index, with the benefit of hindsight from applicant's disclosure, to pick and choose a specific anticancer agent (5-FU), and combine it with Vite, which discloses Compound (1), and then modified 5-FU to capecitabine based upon Miwa. A *prima facie* case of obviousness has not been established as the examiner has not stated any motivation or suggestion to pick 5-FU from the Merck Index, nor has the examiner pointed to any motivation or suggestion for combining Miwa with both Vite and the Merck Index, considering, for example, that Miwa makes no reference to use of 5-FU or capecitabine in combinations. *See Arkie Lures, supra*, 43 USPQ2d at 1297 ("[i]t is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion in the prior art, to combine the elements"); *Smithkline, supra,* 8 USPQ2d at 1475 (the examiner "has the burden to show some teaching or suggestion *in the references* to support their use in the particular claimed combination").

C. NO REASONABLE EXPECTATION OF SUCCESS HAS BEEN PROVIDED BASED ON THE PRIOR ART

To modify or combine the prior art to reject claims as *prima facie* obvious, there must be a reasonable expectation of success in the art. *In re Merck & Co., Inc.*, 800 F.2d

1091, 231 USPQ 375 (Fed. Cir. 1986); *Ex parte Blanc,* 13 USPQ2d 1383 (Bd. Pat. app. & Inter. 1989).

Here, the examiner has not provided any reasonable expectation of success for the combination of Compound (1) and capecitabine as a method of treating cancer with synergistic or enhanced anti-cancer effects. The fact that two anticancer agents might conceivably be combined does not in any way indicate that such a combination will be an effective method of treating cancer. While Miwa states capecitabine may be safer than 5-FU, generally speaking, this does not mean capecitabine and 5-FU are necessarily interchangeable in combinations with other agents which may interact differently with these agents.

Indeed, at the time the application was filed, there were various publications available in the literature counseling against combinations of 5-FU and other microtubule-stabilizing agents, *e.g.*, paclitaxel. For example, in Johnson, K.R. *et al.*, "*5-Fluorouracil Interferes with Paclitaxel Cytotoxicity against Human Solid Tumor Cells*," Clinical Cancer Research, Vol. 3, Issue 10 (1997), at pp. 1739-45, the authors report:

> ... 5-FU actually inhibits the cytotoxic effects of paclitaxel on both mitotic arrest and apoptotic cell death, suggesting that 5-FU might interfere with paclitaxel cytotoxicity at an early stage ....Because recent clinical trials have used a combination of paclitaxel and 5-FU in the treatment of metastatic breast cancers, our results also suggest that the combination of these two drugs might not be as valuable in clinical chemotherapy.

See also Johnson *et al., "5-Fluorouracil Interferes with Taxol Cytotoxicity on Human Solid Tumor Cells,"* Proc. Am. Assoc. Cancer Res., Vol. 38, Meet. 88 *(1997) at* p. 323, reporting that "the 2 agents [5-FU and taxol] have a detrimental effect on the each others action ....".

As another example, WO 01/49287 A1 to Sugen, reports that "the precise mode of action of fluorouracil is not clear," and "[w]hile use of the above combinations [involving 5-FU and various other agents, e.g., methotrexate, leucovorin, interferon, platinum compounds, etc.] is increasing, none of them at present appear to provide a clear advantage over fluorouracil *alone* or fluorouracil in combination with leucovorin." (pp. 41-42).

Various highly significant factors must be considered in making a combination of anti-cancer agents, such as: efficacy of the combination, accumulative side-effects, possible contraindications, and possible interactions between the two anticancer agents. That 5-FU has been previously used in combination therapy with other anticancer agents; and/or that Compound (1) may considered for combination therapy, does not address the issue of providing a reasonable expectation of success. Here, a *prima facie* case of obviousness has not been established as there was no reasonable expectation of success for the combination of Compound (1) and capecitabine as a method of treating cancer at the time the application was filed. Additionally, there was no reasonable expectation of a synergistic or enhanced benefical effect to be achieved with this particular combination of agents.

D. PRIOR ART REFERENCES DO NOT TEACH ALL CLAIM LIMITATIONS

To establish *prima facie* obviousness, all the claim limitations must be taught or suggested by prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CPPA 1974). MPEP 2134.03.

Here, the cited references do not teach or suggest a synergistic or enhanced beneficial combination of Compound (1) and capecitabine, as claimed in claims 117-130. Although Compound (1) is disclosed in Vite, 5-FU is disclosed in The Merck Index, MISC-10 to 11, and capecitabine is disclosed in Miwa, there is no teaching or suggestion in these references regarding a synergistic or enhanced beneficial combination of Compound (1) and capecitabine. Vite discloses only that the compounds of his invention can be combined with known anti-cancer agents and treatments. Likewise, the list of anticancer combinations in The Merck Index does not provide any indication regarding enhanced or synergistic effects of these combinations. Miwa is silent regarding the use of capecitabine and/or 5-FU with a second anticancer drug. As such, the cited references, alone or in combination, do not teach all the limitations of claims 117-130.

POINT THREE

APPELLANT HAS REBUTTED ANY ALLEGED *PRIMA FACIE* OBVIOUSNESS CONCLUSION AS APPLIED TO CLAIMS 117-130 WITH EVIDENCE OF SUPERIOR OR UNEXPECTED RESULTS

As detailed hereinabove in Point One and Point Two, appellant has shown that *prima facie* cases of obviousness have not been established in the two separate rejections as applied to claims 117-125, and claims 117-130. However, even if the requirements for *prima facie* obviousness cases were satisfied, they have been rebutted herein.

Regarding a combination of known agents, the Federal Circuit held that unexpected beneficial results should be considered in determining whether the combination is obvious. *Knoll v. Teva Pharm. USA,* 367 F.3d 1381 (Fed. Cir. 2004). In *Knoll*, at issue was a patent claim to a method of treating pain with a combination of hydrocodone (a/k/a Vicoden®) and ibuprofen. *Id.* at 1383. There was evidence in the case that the prior art had taught combining an opiod, such as hydrocodone, with various NSAIDs, such as ibuprofen. *Id.* at 1384. On this evidence, the district court had enter summary judgment on obviousness. However, the Federal Circuit reversed because there was no "evidence of prior art teaching or suggesting the *enhanced biomedical effect* of the combination of hydrocodone and ibuprofen." *Id.* (emphasis added). The court further concluded that evidence of this enhanced effect should have been considered. *Id.* at 1385.

Here, applicant has submitted evidence of two confirmatory studies, via the Declaration of Dr. Frank Lee, a Ph.D. research scientist, and the inventor herein, demonstrating that Compound (1) in combination with capecitabine produces greater than additive (*i.e.* synergistic) effects in preclinical mouse tumor models. Detailed results in graphical and tabulated form are set forth at paragraphs 12 and 13 of the Lee Declaration. Dr. Lee has provided not only the details regarding his experiments and the particular data collected, but he has analyzed the data and provided his scientific opinion that the results confirmed a surprisingly synergistic effect with this combination of agents. (Lee Declaration, paragraph 9.)

The examiner has alleged that the Declaration does not compare the claimed subject matter with the closest prior art. However, the closest prior art is the anticancer effects of the individual components of the combination. The Declaration contains data for the anticancer effects of the two individual components of the claimed combination and provides a comparison this data with the anticancer effect obtained with the combination therapy. ¶¶14 The results showed a surprisingly synergistic effect for the claimed combination as compared with the closest prior art of Compound (1) monotherapy and capecitabine monotherapy.

Accordingly, evidence of a surprisingly synergistic effect has been sufficiently and convincingly presented to rebut any *prima facie* obviousness rejection. For the foregoing reasons, it is respectfully requested that the Section 103(a) rejection of claims 117-130 be withdrawn.

POINT FOUR

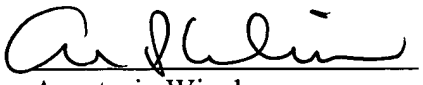
APPELLANT HAS REBUTTED ANY ALLEGED *PRIMA FACIE* OBVIOUSNESS CONCLUSION AS APPLIED TO CLAIMS 126-130 WITH EVIDENCE OF SUPERIOR OR UNEXPECTED RESULTS

The examiner has applied separate grounds of rejection as to claims 117 to 125, and claims 117 to 130. Presumably, the first ground of rejection (discussed in Point One), was applied only to claims 117 to 125 (placed in one group), and not to claims 126 to 130, because the latter set of claims recite a synergistic anti-cancer effect, whereas claims 117 to 125 recite an enhanced beneficial anti-cancer effect and do not specifically recite synergy. Applicants submit that the rebuttal evidence discussed in Point Three, *supra*, is applicable to all claims on appeal, but also that the evidence should be separately applied and considered as to claims 126 to 130. Accordingly, even if the requirements for *prima facie* obviousness cases were satisfied as to claims 126 and 130, they have been rebutted herein, for the reasons discussed in Point Three. For the foregoing reasons, it is respectfully requested that the Section 103(a) rejection of claims 126-130 be withdrawn.

CONCLUSION

For all the reasons set forth herein, appellant respectfully submits that the rejections of claims 117-130 are erroneous and request that the Board overturn them.

Respectfully submitted:



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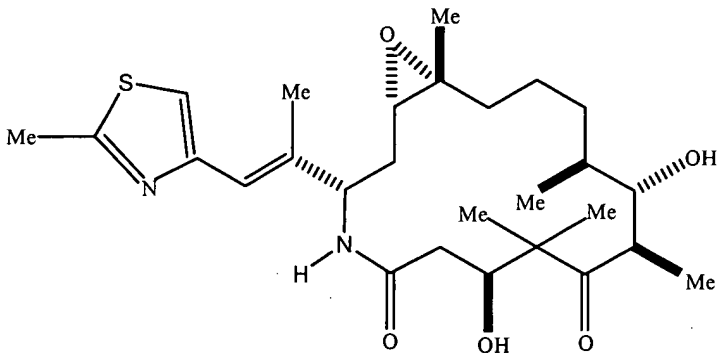
Date: May 25, 2006

VIII. CLAIMS APPENDIX

(Appealed Claims 117-130)

117. A method of treating cancer in a mammal selected from metastatic breast cancer, lung cancer, pancreatic cancer, ovarian cancer, prostate cancer, colon cancer, and/or small cell lung cancer, comprising administering to the mammal a therapeutically-effective combination of (1) a dosage unit of capecitabine and (2) a dosage unit of Compound (1), having the formula,



or a pharmaceutically-acceptable hydrate, solvate, or geometric, optical, or stereoisomer of Compound (1), wherein the administration will provide a greater anti-cancer effect than the effect obtainable with either the dosage unit of capecitabine or the dosage unit of Compound (1) alone.

118. The method of claim 117 wherein the cancer is metastatic breast cancer refractory to taxane treatment.

119. The method of claim 117 wherein the cancer is metastatic breast cancer resistant to taxane treatment.

120. The method of claim 117 wherein the cancer is metastatic breast cancer sensitive to taxane treatment.

121. The method according to claim 117, wherein the capecitabine is administered following the administration of Compound 1.

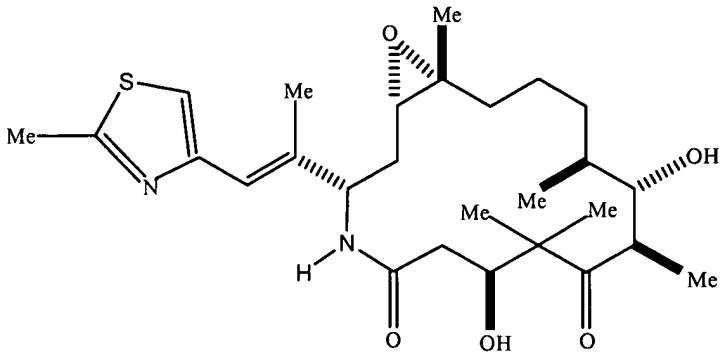
122. The method according to claim 117, wherein the capecitabine is administered before the administration of Compound 1.

123. The method according to claim 117, wherein the capecitabine is administered substantially simultaneously with the administration of Compound 1.

124. The method according to claim 117, wherein the capecitabine is administered orally and the Compound 1 is administered parenterally.

125. The method according to claim 117, wherein the capecitabine is administered orally and the Compound 1 is administered orally.

126. A method of treating cancer in a mammal selected from metastatic breast cancer, lung cancer, pancreatic cancer, ovarian cancer, prostate cancer, colon cancer, and/or small cell lung cancer, comprising administering to the mammal a synergistically-effective combination of capecitabine and Compound (1), having the formula



or a pharmaceutically-acceptable hydrate, solvate, or geometric, optical, or stereoisomer of Compound (1).

127. The method of claim 126, wherein the cancer is metastatic breast cancer.

128. The method of claim 126 wherein the cancer is refractory to taxane treatment.

129. The method of claim 126 wherein the cancer is resistant to taxane treatment.

130. The method of claim 126 wherein the cancer is sensitive to taxane treatment.

(IX) EVIDENCE APPENDIX

Copy of The Merck Index, (12th ED), 1996, pages MISC-10 and 11.

Declaration of Francis Lee, filed October 27, 2005.

THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

TWELFTH EDITION

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Joanne F. Kinneary, *Assistant Editor*

Published by
Merck Research Laboratories
Division of
MERCK & CO., INC.
Whitehouse Station, NJ

1996

Cancer Chemotherapy Drug Regimens

Listed below are selected acronyms for combination cancer chemotherapy regimens comprising substances in *The Merck Index*.

Acronym	Drug regimens
ABP	doxorubicin + bleomycin + prednisone
ABVD	doxorubicin + bleomycin + vinblastine + dacarbazine
AC	doxorubicin + cyclophosphamide
ACVB	doxorubicin + cyclophosphamide + vindesine + bleomycin
ADIC	doxorubicin + dacarbazine
APO	doxorubicin + prednisone + vincristine + 6-mercaptopurine + asparaginase + methotrexate
AV	doxorubicin + vincristine
BACOP	bleomycin + doxorubicin + cyclophosphamide + vincristine + prednisone
BAPP	bleomycin + doxorubicin + cisplatin + prednisone
BCD	methotrexate + doxorubicin + cisplatin
BCVPP	carmustine + cyclophosphamide + vinblastine + procarbazine + prednisone
BEP	bleomycin + etoposide + cisplatin
BMP	bleomycin + methotrexate + cisplatin
BOLD	bleomycin + vincristine + lomustine + dacarbazine
CA	cyclophosphamide + doxorubicin
CAF	cyclophosphamide + doxorubicin + fluorouracil
CAMF	cyclophosphamide + doxorubicin + methotrexate + fluorouracil
CAP	cyclophosphamide + doxorubicin + cisplatin
CAP-BOP	cyclophosphamide + doxorubicin + procarbazine + bleomycin + vincristine + prednisone
CAV	cyclophosphamide + doxorubicin + vincristine
CAVE	cyclophosphamide + doxorubicin + vincristine + etoposide
CAVEP	cyclophosphamide + doxorubicin + vincristine + etoposide + cisplatin
CBV	cyclophosphamide + carmustine + etoposide
CC	carboplatin + cyclophosphamide
CFP	cyclophosphamide + fluorouracil + prednisone
CFPMV	cyclophosphamide + fluorouracil + prednisone + methotrexate + vincristine
CFPT	cyclophosphamide + fluorouracil + prednisone + tamoxifen
CHAD	cyclophosphamide + hexamethylmelamine + doxorubicin + cisplatin
CHAMOCA	cyclophosphamide + hydroxyurea + dactinomycin + methotrexate + vincristine + doxorubicin
CHAP-5	cyclophosphamide + hexamethylmelamine + doxorubicin + cisplatin
CHF	cyclophosphamide + hexamethylmelamine + fluorouracil
ChlVPP	chlorambucil + vinblastine + procarbazine + prednisone
CHO	cyclophosphamide + doxorubicin + vincristine
CHOP	cyclophosphamide + doxorubicin + vincristine + prednisone
CHOP-B	cyclophosphamide + doxorubicin + vincristine + prednisone + bleomycin
CMF	cyclophosphamide + methotrexate + fluorouracil
CMFP	cyclophosphamide + methotrexate + fluorouracil + prednisone
CMFVP	cyclophosphamide + methotrexate + fluorouracil + vincristine + prednisone
C-MOPP	cyclophosphamide + mechlorethamine + vincristine + procarbazine + prednisone
CMV	cisplatin + methotrexate + vinblastine
COAP	cyclophosphamide + vincristine + cytarabine + prednisolone
CODE	cisplatin + vincristine + doxorubicin + etoposide
COMLA	cyclophosphamide + vincristine + methotrexate* + cytarabine
COMP	cyclophosphamide + vincristine + methotrexate + prednisone
COP	cyclophosphamide + vincristine + prednisone
COP-BLAM	cyclophosphamide + vincristine + prednisone + bleomycin + doxorubicin + procarbazine
COPP	cyclophosphamide + vincristine + prednisone + procarbazine
CVF	cyclophosphamide + vincristine + fluorouracil
CVP	cyclophosphamide + vincristine + prednisone
CYVADIC	cyclophosphamide + vincristine + doxorubicin + dacarbazine
DICEP	cyclophosphamide + etoposide + cisplatin
EAP	etoposide + doxorubicin + cisplatin
EFP	etoposide + fluorouracil + cisplatin
ELF	etoposide + leucovorin + fluorouracil
EMA-CO	etoposide + methotrexate + dactinomycin + cyclophosphamide + vincristine
ESHAP	etoposide + methylprednisolone + cytarabine + cisplatin
FA	fluorouracil + doxorubicin
FAC	fluorouracil + doxorubicin + cyclophosphamide
FAM	fluorouracil + doxorubicin + mitomycin C
FAMTX	fluorouracil + doxorubicin + methotrexate
FAP	fluorouracil + doxorubicin + cisplatin
FEB	fluorouracil + epirubicin + carmustine
FUVAC	fluorouracil + vinblastine + doxorubicin + cyclophosphamide
HAD	hexamethylmelamine + doxorubicin + cisplatin
H-CAP	hexamethylmelamine + cyclophosphamide + doxorubicin + cisplatin

Cancer Chemotherapy Drug Regimens (Continued)

Acronym	Drug regimens
Hexa-CAF	hexamethylmelamine + cyclophosphamide + methotrexate + fluorouracil
ICE	ifosfamide + carboplatin + etoposide
LOPP	chlorambucil + vincristine + procarbazine + prednisone
LSA_2-L_2	cyclophosphamide + vincristine + prednisone + daunorubicin + methotrexate + cytarabine + thioguanine + colaspase + hydroxyurea + carmustine
MAC	methotrexate + dactinomycin + chlorambucil
MACC	methotrexate + doxorubicin + cyclophosphamide + lomustine
MACOP-B	methotrexate* + doxorubicin + cyclophosphamide + vincristine + prednisone + bleomycin
M-BACOD	methotrexate + bleomycin + doxorubicin + cyclophosphamide + vincristine + dexamethasone
MBD	methotrexate + bleomycin + cisplatin
MCF	mitoxantrone + cyclophosphamide + fluorouracil
MINE	mesna + ifosfamide + mitoxantrone + etoposide
MIP	mitomycin + ifosfamide + cisplatin
MOP	mechlorethamine + vincristine + procarbazine
MOPP	mechlorethamine + vincristine + procarbazine + prednisone
M-VAC	methotrexate + vinblastine + doxorubicin + cisplatin
MVP	mitomycin + vindesine + cisplatin
MVPP	mechlorethamine + vinblastine + procarbazine + prednisone
PAC	cisplatin + doxorubicin + cyclophosphamide
PC	cisplatin + cyclophosphamide
PCV	procarbazine + lomustine + vincristine
PE	cisplatin + etoposide
PEB	cisplatin + etoposide + bleomycin
PMF	cisplatin + mitomycin C + fluorouracil
ProMACE	prednisone + methotrexate + doxorubicin + cyclophosphamide + etoposide
ProMACE-CytaBOM	prednisone + methotrexate + doxorubicin + cyclophosphamide + etoposide + cytarabine + bleomycin + vincristine + methotrexate*
ProMACE-MOPP	prednisone + methotrexate* + doxorubicin + cyclophosphamide + etoposide + mechlorethamine + vincristine + procarbazine + prednisone
PVB	cisplatin + vinblastine + bleomycin
SMF	streptozocin + mitomycin + fluorouracil
VAB-6	vinblastine + dactinomycin + bleomycin + cisplatin + cyclophosphamide
VAC	vincristine + dactinomycin + cyclophosphamide
VAD	vincristine + doxorubicin + dexamethasone
VAMP	vincristine + prednisone + methotrexate + 6-mercaptopurine
VAP-cyclo	vincristine + doxorubicin + prednisolone + cyclophosphamide
VIP	vindesine + ifosfamide + cisplatin
VMF	etoposide + methotrexate + fluorouracil
VP	vindesine + cisplatin

*with folinic acid (leucovorin) rescue

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450..

Anastasia P. Winslow		October 27, 2005
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
LEE
APPLICATION NO: **10/091,061**
FILED: **MARCH 5, 2002**
FOR: **COMBINATION OF EPOTHILONE ANALOGS AND CHEMOTHERAPEUTIC AGENTS FOR THE TREATMENT OF PROLIFERATIVE DISEASES**

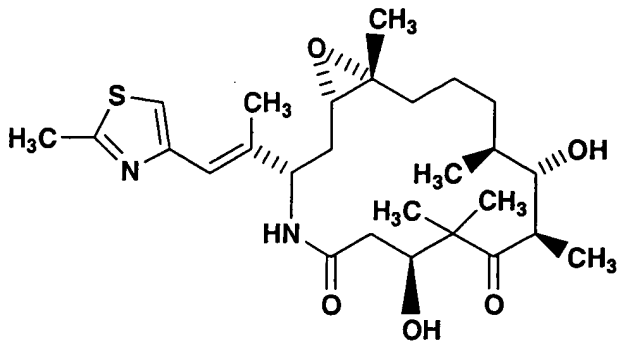
Art Unit: **1617**
Examiner: JIANG, SHAOJIA A

DECLARATION OF FRANCIS LEE

1. I am a Ph.D. research scientist employed with Bristol-Myers Squibb Company, in Princeton, New Jersey.

2. I have thirteen years of full-time experience in the pharmaceutical industry, including experience with preclinical models and evaluating compounds for oncological use based on preclinical *in vitro* and *in vivo* studies.

3. My work at BMS has involved preclinical studies related the aza-epothilone B analog, ixabepilone, which has the chemical structure:

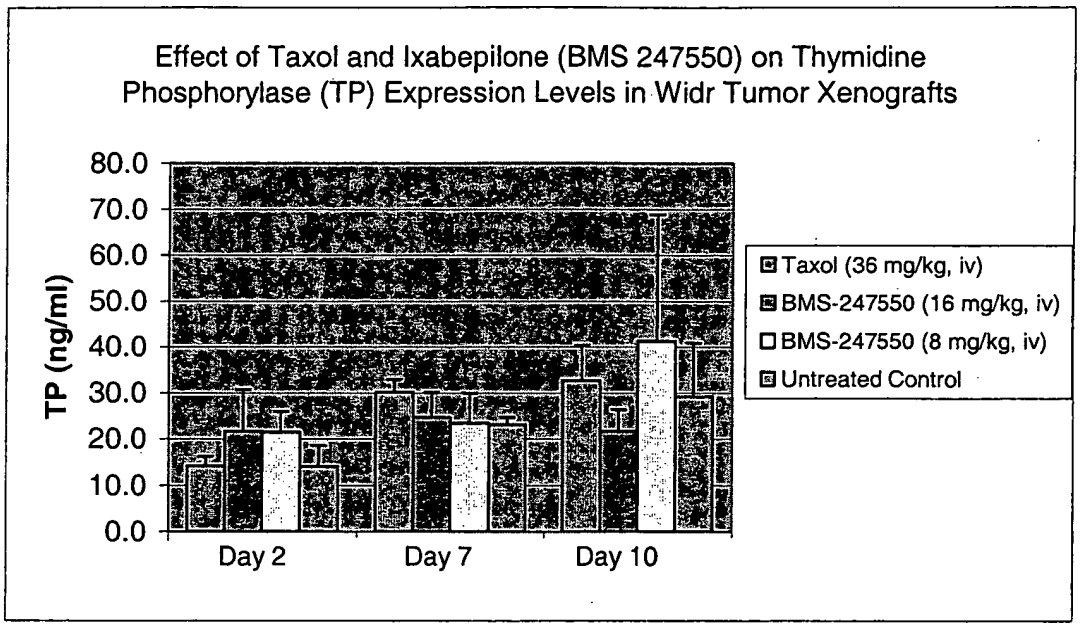


4. I am a named inventor on the instant patent application which claims combinations of ixabepilone and capecitabine. I make this Declaration in support of the patent claims to this combination of agents.

5. In 1998, a journal article was published by Sawada *et al.*, "*Induction of Thymidine Phosphorylase Activity and Enhancement of Capecitabine Efficacy by Taxol/Taxotere in Human Cancer Xenografts*," Clinical Cancer Research, Vol. 4, pp. 1013-1019, April 1998. This article reported that Taxol, Taxotere, and mitomycin C greatly increased levels of human thymidine Phosphorylase (TPs), in a WiDr human colon carcinoma xenograft tumor model (p. 1013). The TPs enzyme is known to be essential in triggering the conversion of the prodrug, capecitabine, to its active form, 5 fluorouracil. In this article, the authors reported that capecitabine is greatly modulated by TPs and that Taxol and Taxotere might enhance the efficacy of capecitabine by upregulating TPs (p. 1016). However, the authors reported that "the toxicity of Taxol/Taxotere and capecitabine does not appear to be synergistic, although the efficacy of these compounds in combination was additive to synergistic" (p. 1018).

6. Following review of this journal article, studies were performed to evaluate the effect of Taxol and ixabepilone on the induction of TPs levels in the WiDr human colon carcinoma xenograft model. In particular, a test was performed in which WiDr tumors were implanted subcutaneously using tumor fragments obtained from donor mice. The tumors were allowed to grow to a pre-determined size of 150-300 mg. The animals were then evenly distributed to various treatment and control groups. Treatment of each animal was based on individual body weight on a mg/kg basis. Taxol was administered at the efficacious dose of 36 mg/kg/inj (daily, via intravenous injection [IV]) and ixabepilone (BMS-247550) was administered at dose levels of 16 and 8 mg/kg/inj (daily, via IV). Tumors (3 samples per treatment group and time point) were then harvested on day 2, day 7, and day 10-post drug administration and the relative level of TP in each sample was determined.

7. Results of the above-referenced study are set forth below. As can be seen in the below figure, it was determined that Taxol showed a slight increase in TP levels compared to untreated control on day 7 post-treatment (1.31-fold increase versus untreated control, $p < 0.05$). However, on day 2 or day 10 post-treatment, TP levels were indistinguishable from untreated control. Ixabepilone (BMS 247550), at both dose levels failed to significantly increase TP level over untreated controls on either day 2, day 7, or day 10.



8. From the above results, I expected that ixabepilone would *not* have a synergistic effect in combination with capecitabine in preclinical tumor cell models. This expectation stemmed from the fact that TP is essential to trigger the conversion of capecitabine to 5-FU, and the studies demonstrated that ixabepilone failed to significantly increase TP levels in the above-referenced xenograft tumor model.

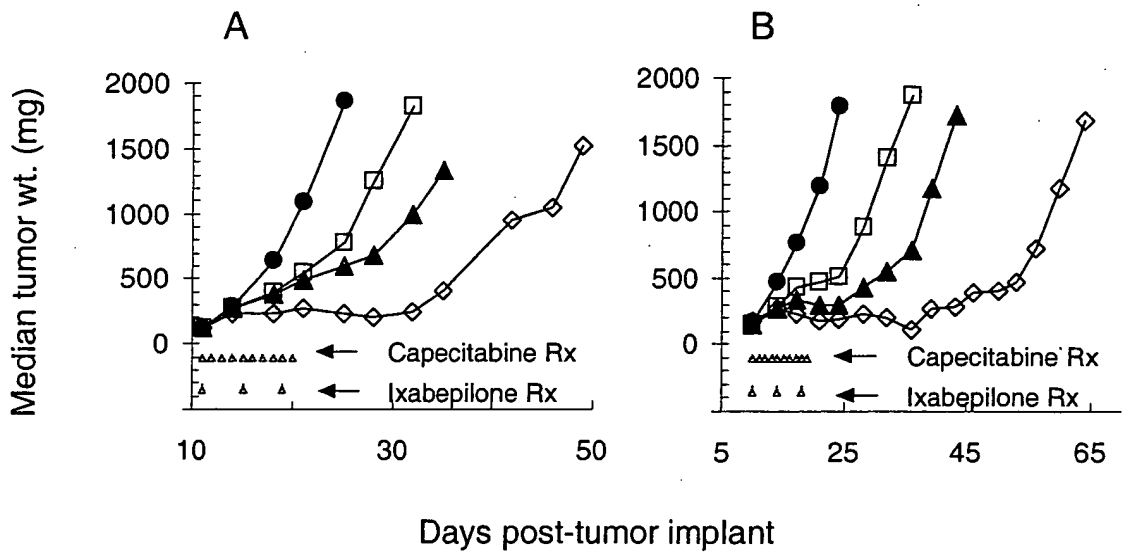
9. Contrary to my expectation and surprisingly, I discovered a synergistic effect is obtained in preclinical studies involving the administration of ixabepilone and capecitabine in combination.

10. For example, despite the results obtained from the TP up-regulation study, discussed above, the human colon carcinoma cell line GEO was used to evaluate the combined efficacy of ixabepilone and capecitabine in two repeated studies. In these two studies, human tumors were

propagated as subcutaneous transplants in an appropriate mouse strain using tumor fragments obtained from donor mice. In one study, single agent ixabepilone alone was administered to one group of tumor-implanted mice at its maximum tolerated dose (MTD) of 10 mg/kg, via an intravenous injection (IV), three times once every four days (Q4D x 3). In a second group of tumor-implanted mice, capecitabine alone was administered at its MTD, namely, 250 mg/kg/adm, administered orally (PO) once every (Q) day (D) for ten consecutive days (QD x 10). In a third group of mice, the two agents were administered together, *i.e.*, capecitabine at 250 mg/kg/adm, QD x 10 (orally) in combination with ixabepilone at 10 mg/kg/adm., Q4D x 3 (via IV). The tumor growth during the course of administration was measured and compared with tumor growth of a control group of mice, receiving tumor implants and no chemotherapeutic treatment. From the studies, it was determined that combination of the two agents surprisingly produced preclinical therapeutic synergism, yielding anti-tumor efficacy that was superior to either of the single agents alone at their MTDs. Similar results were obtained in an independent confirmatory study.

12. More specifically, the two graphs below represent results that were obtained from the two independent studies comparing the effects of monotherapy involving either ixabepilone or capecitabine, as compared with a combination therapy involving these two agents together. In these figures, each symbol represents the median tumor burden of a group of 8 mice. The symbol (●) represents results from the control group; the symbol (□) represents results from the capecitabine alone group (250 mg/kg/adm, QD x 10, PO); the symbol (▲) represents results

from the ixabepilone alone group (10 mg/kg/adm, Q4D x 3, IV); and lastly, the symbol (◇) represents the results achieved with the mice receiving the combination therapy of capecitabine (250 mg/kg/adm, QD x 10, PO), and ixabepilone (10 mg/kg/adm, Q4D x 3, IV). When administered on the same day, the two agents were given more or less simultaneously (ixabepilone preceded capecitabine by less than 1 hr).



13. The below table provides the results from the two studies in numerical form wherein the term "MTD" refers to the maximum tolerated dose, the letter "Q" means daily, the term "PO" means orally administered, and "LCK" refers to "gross log 10 cell kill", which is a measure of tumor response (tumor cell kill).

Antitumor efficacy of Combined Chemotherapy with Ixabepilone and Capecitabine Versus the GEO Human Colon Carcinoma

	Treatment		Efficacy/Toxicity			
	Ixabepilone Dose[a,b]	Capecitabine Dose[a,c]	Tumor Growth Delay[d]		Wt. Change	
Study	(mg/kg)	(mg/kg)	(LCK)	(days)	(g)	P[e]
No. 1	10	-	0.8	11	-3.8	0.035
	-	250	0.4	5.5	0.2	0.0004
	10	250	1.9	25.2	-4.9	-
No. 2	10	-	1.2	18.7	-4.2	0.0037
	-	250	0.6	9.7	-0.3	0.0038
	10	250	3.9	62	-4.2	-

[a] MTD; [b] Regimen: = IV, Q4D x 3; [c] Regimen: = PO, QD x 10; [d] Target tumor size = 1000 mg;
[e] P value is for comparison with the combination group

14. As can be seen from the above graphs and tabulated data, the delay in tumor growth when ixabepilone and capecitabine were administered in combination was more than additive as compared with monotherapy involving either agent alone. For example, in Study No. 1, anti-tumor efficacy obtained with the combination (LCK = 1.9) was greater than that achieved with either agent alone, even when the monotherapy effects are combined (0.8 + 0.4), and the period of growth delay was also more than additive for the combination (*i.e.*, delay of 25.2 days for the combination therapy, as compared with delay of 11 + 5.5 days for the combined single agent therapies.) In Study No. 2, again, anti-tumor efficacy obtained with the combination (LCK = 3.9) was greater than that achieved with either agent alone, even when the monotherapy effects are combined (1.2 + 0.6), and the period of growth delay was also more than additive for the

combination (*i.e.*, delay of 62 days for the combination therapy, as compared with 18.7 +9.7 days for the combined single agent therapy.)

15. In my opinion, the above studies demonstrated a synergistic effect is obtained in preclinical studies involving the administration of ixabepilone and capecitabine, in combination, and I found this synergistic effect to be surprising, particularly given our previous study which demonstrated that ixabepilone did not upregulate TPs.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant Application or any patent issuing therefrom.

Dated: 10/26/2005
(Month/Day/Year)

Francis Lee

(x) RELATED PROCEEDINGS APPENDIX

-No Entry-